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p53 and the CNS

Tumors and Developmental Abnormalities

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Abstract

This article reviews the recent molecular and clinical studies that characterize the role of p53 in pathologies of the central nervous system, p53 has many important biological functions, notably, maintenance of DNA stability and regulation of apoptosis. These features are essential to avoid cellular transformation and ensure normal brain development. Lack of p53 function in the brain results in tumor formation in the astrocytic and lymphoid lineages and in severe neurodevelopmental diseases, such as exencephaly.

Index Entries: Brain development; central nervous system; tumor suppressor gene; glioma; anencephaly.

Introduction

p53 is a protein with a very large spectrum of biological and physiological functions including safeguard of genomic stability, cell cycle regulation, cell differentiation, apoptosis, and angiogenesis (*1,2*).

p53 primarily acts as a transcription factor, but can also interact with other proteins making it an important player in different cellular pathways. p53 is involved in regulating the cell cycle and maintaining the genome's integrity. Consequently, p53 malfunction has been related to tumor formation. p53 is a tumor suppressor, as its loss of activity is associated with more than 50% of human tumors, including primary brain tumors of astrocytic and lymphoid origin. Nevertheless, tumors are not the only type of brain pathologies in which p53 is involved. Recent data have shown neuronal developmental defects in p53 null mice, such as exencephaly.

In this article we present the structure of the *TP53* gene and describe in detail the biochemical aspects and biological functions of its gene product. Maintenance of genomic stability, cell

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cycle regulation, control over differentiation, and apoptosis of central nervous system (CNS) cells are all determinant in avoiding glioma formation and CNS malformations.

p53 Gene and Protein

TP53 *Gene Structure*

The *TP53* gene consists of 11 exons and 10 introns (Fig. 1A) spanning 20 kb of genomic DNA on the short arm of chromosome 17, at 17p13.1 (*3*). *TP53* encodes a 2.8 kb mRNA, which is translated into a 53-kDa nuclear phosphoprotein that acts as a transcription factor (*4,5*) and functions as a tumor suppressor (*6*).

Regulation of TP53 *Gene Expression*

Different regulatory sites have been mapped in the 5′ upstream region of the *TP53* gene, in exon 1 and in intron 1 (*7*). Analysis of the *TP53* promoter region evidenced the lack of TATA and CAAT sequences and the presence of different recognition sites for oncogenic transcription factors such as NF1, jun (*8*), and Myc/Max (*9*).

p53 may have autoregulatory functions: responsive elements are present on the *TP53* promoter and reporter constructs under the control of these elements are downregulated by p53 (*10*). Nevertheless, there is still no evidence for p53 binding to its own promoter.

Recently, a PAX-5 binding site was identified within the untranslated first exon of *TP53* (*11*). PAX genes encode nuclear transcription factors implicated in the control of mammalian embryogenesis. In particular, PAX-2, 5, and –8 are highly expressed during the development of the CNS. It has been hypothesized that PAX-5 may have a physiological downregulatory function on *TP53* expression in order to allow proliferation of stem cells that migrate from the ventricular zone to the intermediate zone of the neural tube. Stuart et al. (*11*) reported that PAX-5 is often overexpressed in high-grade gliomas, suggesting that constitutive expression of PAX-5 may allow tumors to bypass the need for p53 mutation to abrogate p53-mediated processes. However, subsequent work failed to show a correlation between PAX5 expression and p53 status in a series of patients showing recurrence from low-grade astrocytoma to glioblastoma (E.T. Stuart and E. G. Van Meir, unpublished data). In addition, whereas PAX5 overexpression was confined to late stage glioblastoma, p53 mutations are known to occur early in the progression of astrocytoma.

Other proteins identified as potential inducers of *TP53* transcription are ETS1 and ETS2 factors (*12*) and the C7 poxviral transcription factor (*13*).

p53 Protein

Functional p53 is a nonglobular tetramer of a single peptidic chain that comprises three functionally characterized segments (Fig. 1C): the N-terminal transcription activation region, a central core responsible for specific DNA binding and a C-terminal oligomerization sequence.

Exon 11 of p53 mRNA codes for the very C-terminal region of the protein that is a negative regulator of the protein's activity (*14*). This terminal segment of p53 seems to interact somehow with the core of the protein and prevents p53-DNA binding. This allosteric model for negative regulation of p53 activity by the C-terminus is confirmed by different experimental data showing that disruption of this interaction, by both physiological and artificial events, induces a conformational change that results in p53 activation (*14,15*).

Moreover, five highly conserved and independently folding domains (I–IV) can be distinguished in the p53 protein (Fig. 1C).

Crystallography shows that the central core of p53 is a sandwich of two antiparallel β sheets formed of four and five β strands and a loop sheet helix motif packed against the β sandwich (*16*). The overall structure of the β sandwich is stabilized by two large loops held together by a Zn atom.

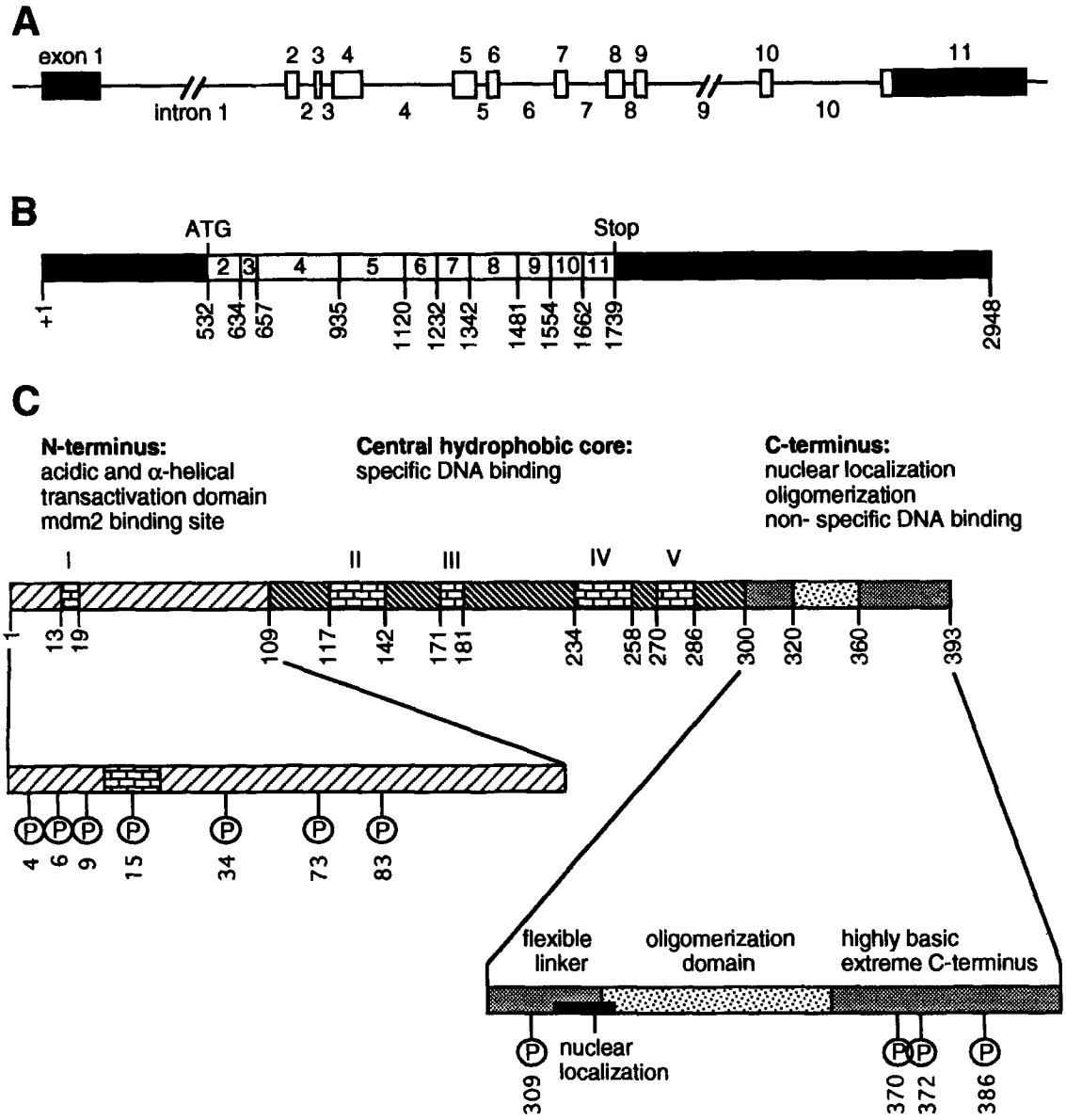

Fig. 1. Schematic representation of the p53 gene, mRNA and protein structures. **(A)** *TP53* gene structure: boxes stand for exons (white parts are translated, black ones are not) and segments for introns. Numbers of exons and introns are indicated. **(B)** mRNA structure: nucleotide positions at splicing junctions of exons 1–11 are indicated. Start (ATG) and stop codons are also shown. The predicted protein size from mRNA is 43.5 kDa. **(C)** Protein structure: amino acid localization of the five evolutionarily conserved domains (I–V) are shown. Enlargements of the N- and C-termini show the phosphorylation sites in the mouse (human phosphorylation sites are similar) and the distinct functional domains.

Although the β sandwich is an uncommon structure for transcription factors, the loop sheet helix and the two large loops are typical motifs of proteins capable of complexing with DNA. In fact, crystallographic studies of the p53/DNA complex demonstrated that the loop sheet helix motif binds to the DNA's major groove. One of the loops binds to the minor groove, and the other has an important role in stabilizing the overall structure of the complex.

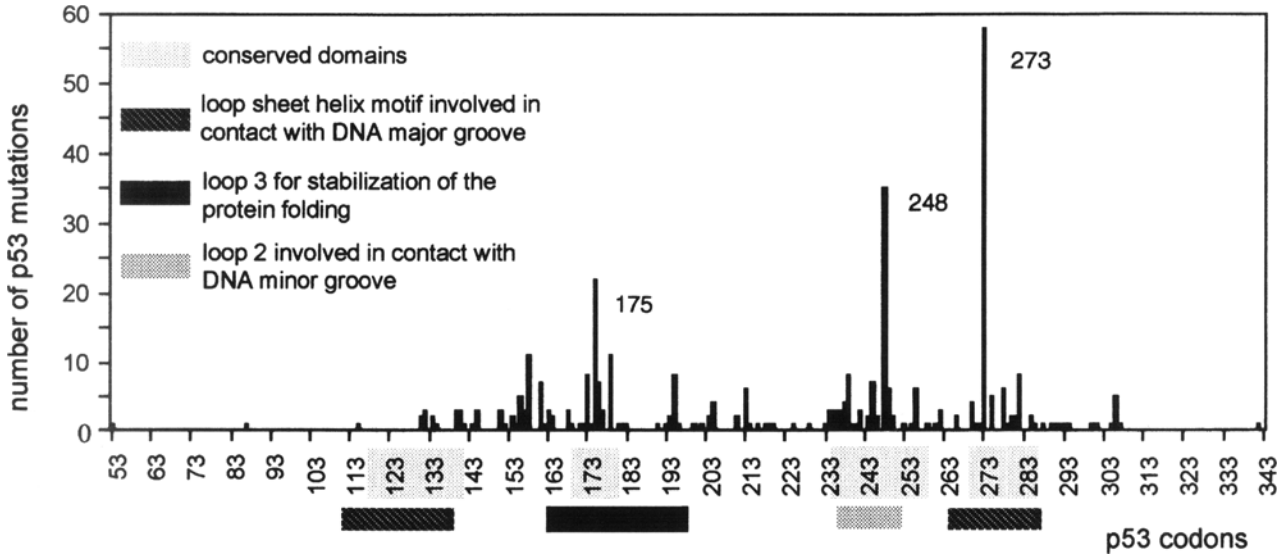

Fig. 2. Frequencies of p53 exon mutations found in brain tumors reported by the IARC database: http://www.iarc.fr. Regions implicated in DNA interaction and protein stability as well as the conserved domains of the protein are indicated.

Moreover, it has been demonstrated that these motifs are the sites of the most frequently mutated p53 codons found in tumors and correspond to the highly conserved domains of the protein, suggesting that these regions have a biological importance (Fig. 2).

p53 accomplishes its biological roles either by interaction with other proteins or acting as a transcription factor. It enhances transcription of specific genes by binding to promoters containing four copies of the p53 pentameric consensus sequence PuPuPuC(A/T)-(T/A)GPyPyPy with a stoichiometry of one core domain for one pentamer (*17*).

Three factors have been shown to act as p53 coactivators and potentiate its transcriptional activity: the nuclear tyrosine kinase c-*abl* (*18*) and the two homologous transcription factors p300 and CBP, all of which are implicated in cell proliferation and differentiation. The synergistic transcription activity of p300/CBP and p53 is permitted by physical interaction between the proteins (*19–21*). More recent data indicate that acetylation of the p53 C-terminal domain by its coactivator p300 dramatically increases sequence-specific DNA binding of p53 (*22*) (Fig. 3).

p53 is also able to repress transcription of genes containing TATA boxes by binding, through its oligomerization domain, to the TATA binding protein (TBP) and preventing its interaction with DNA (*23*). Although it has been shown that genes that have neither TATA boxes nor p53 consensus sequences are not submitted to direct p53 regulation (*24*), more recent data indicate that p53 inhibits the transcription of genes containing an AP1 site by sequestering the transcription factor p300 (*19*).

Regulation of p53 Activity

Responses to Physiological Stress

p53 is a sensor of a variety of physiological stress conditions to the cell such as hypoxia, heat and starvation (*25,26*). The response to such insults is either growth arrest or apoptosis (Fig. 3). Graeber et al. (*25*) compared the mechanisms and the effects of p53 induction by different types of stress. Their experiments

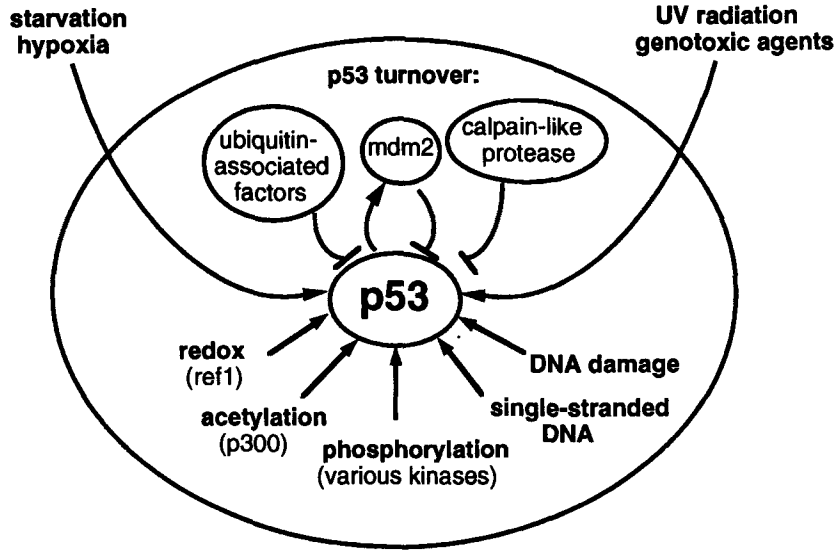

Fig. 3. Schematic representation of factors regulating p53 activity. *Arrows,* induction; T-bars indicate repression.

showed that heat induces a mutant conformation on p53 allowing it to complex with heat shock protein hsc70 and to increase its half-life. This is accompanied by cytoplasmic instead of nuclear p53 accumulation during high temperature shifts. On the other hand, p53 accumulates in the nucleus during hypoxia, and an increased p53 transactivational activity can be observed. Recent data also suggest that p53 might be stabilized by an interaction with hypoxia inducible factor (HIF-1) (*27*).

Sensing of DNA Damage

DNA damaging agents such as ionizing radiation (*28*) and genotoxic and antimicrotubule agents (*29,30*) induce p53 expression (Fig. 3). The precise sequence of events that link DNA damage to p53 induction is unknown, but involves the ATM gene product (*31*) and the DNA repair machinery. Within this context, it is interesting to mention the capacity of p53 to bind repair proteins XPD and XPB (*32*). Moreover, in vitro experiments have shown that single stranded DNA, within the size range generated during excision repair, stimulates p53–DNA binding (*33–35*).

When increased, p53 may function as a tumor suppressor by inducing tumor cell apoptosis. This in turn may lead to clonal selection in vivo of cells lacking wild-type (wt) p53 (*36*). As a consequence, anticancer treatments inducing necrosis and DNA damage, such as radio- and chemotherapy, could also favor the expansion of p53 mutated cells and induce malignant progression (*37*).

Phosphorylation

p53 has multiple phosphorylation sites both in its N- and C-termini (Fig. 1C). The N-terminal phosphorylation seems to be preferentially accomplished by cyclin-dependent kinases, double-stranded DNA activated protein kinase, mitogen-activated protein kinase, Jun N-terminal kinase and Raf kinase; whereas the C-terminal domain is phosphorylated by cyclin-dependent kinases, casein kinase II, protein kinase C (PKC), and the CDK7-cyclinH-p36 complex of TFIIH (*38–40*).

Even though there is considerable evidence that phosphorylation regulates p53 activity in vivo (*41*), it is unclear how the cited kinases affect p53. Different single p53 phosphoryla-

tion mutants were tested for their transcription activity and for their capacity to suppress cell proliferation, but no difference was found in comparison with wt p53 (*42*). By contrast, in some cases, altering two or more phosphorylation sites at once could significantly lessen p53 transactivation potential or DNA binding, or both (*40*).

Furthermore, the conformation of p53 is determinant for its availability as a substrate for different kinases and for the phosphorylation pattern generated by the same kinase (*43*). This information is coherent with the observation that the phosphorylation status of human p53 at serines 15 and 392 was found to be different between the wt and a conformational mutant p53 in glioblastoma cells. In particular, phosphorylation of serine 15 was reduced in the mutant p53 compared with wt, while phosphorylation of ser 392 was increased (*44*).

Taken together, these data indicate that it is not possible to consider phosphorylation as a simple on/off switch for p53 functions, but it is rather a complex regulatory system that could also be cell type dependent. Recent data indicate that phosphorylation of N-terminal serines 15 and 37 by DNA-PK is induced after DNA damage and inhibits p53 interaction with MDM2, resulting in p53 activation (*45*). Phosphorylation of the C-terminus of p53 by casein kinase II was also shown to activate p53-DNA binding in vitro (*14*). Moreover, p53 hyperphosphorylation by oncogene activation of the MAPK pathway may be the molecular basis for the ability of p53 to sense oncogene transformation in the cell and exert its antioncogenic effect (*46*).

Redox State of the Protein

Another effector of p53 activity is the redox state of the protein (Fig. 3). It is now appreciated that oxydization renders p53 unable to bind DNA, whereas reduction enhances this capacity. According to this idea, the redox repair protein Ref 1, which was shown to activate AP-1 by reducing a conserved cystein in its DNA binding domain, has been recently identified as a potent activator of p53 both in a redox-dependent and an -independent manner (*47,48*).

MDM2 Binding

The activity of p53 is downregulated in an autoregulatory feedback loop: p53 induces the transcription of the *MDM2* gene and the accumulation of the oncoprotein mdm2 represses p53 (Fig. 3). The delay between p53 induction and *MDM2* activation defines the time during which p53 can exert its activity (*49,50*). This mechanism is used by certain tumors, including osteosarcomas (*51*) and about 10% of astrocytomas (*52*) to inactivate p53 by *MDM2* gene amplification. A novel player in p53 regulation was identified recently: $p14^{ARF}$, the product of a gene commonly deleted in human cancer, was found to inhibit mdm2 function. The absence of $p14^{ARF}$ increases the availability of mdm2 for p53 downregulation, which should favor cellular transformation (*53*).

p53 Turnover

The most apparent and important regulatory mechanism of the activity displayed by p53 is its rapid turnover (half-life of about 20–30 min), which limits the quantity of wt p53 in the nucleus (Fig. 3).

One of the mechanisms that regulate p53 turnover is the ubiquitin-dependent pathway (Fig. 3). In human papillomavirus-infected cells a tripartite complex forms between the viral protein E6, p53, and the cellular protein E6-AP and targets p53 for ubiquitin-dependent proteolysis (*54*). Accordingly, p53 was shown to accumulate in cell lines lacking ubiquitin-dependent mechanisms (*55*). Nevertheless, the precise molecular mechanisms of this pathway and its general applicability are unclear.

Recent experiments suggest that p53 turnover may also be accomplished by an ubiquitin degradation pathway independent of E6-AP. It was shown that E6-AP has no effect on p53 levels in nonvirus-infected cells (*56*) and that mdm2 is able to induce p53 degradation by a proteasome complex (*57,58*). These data are confirmed by recent results showing that p53 mutants that are unable to bind mdm2 are more stable than other p53 mutants or the wt protein. Moreover, treatment of tumor cells containing

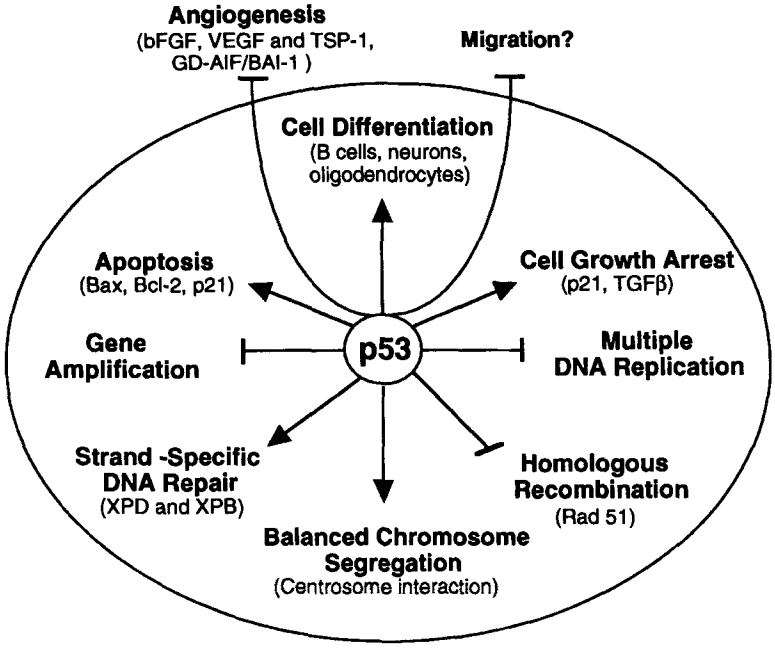

Fig. 4. Schematic representation of p53 functions. *Arrows,* induction; T-bars indicate inhibition.

wt p53 with agents that disrupt the p53–mdm2 interaction induces p53 accumulation (*59*).

Finally, a completely different mechanism for p53 degradation has been recently observed. In this case, p53 turnover is regulated by a calpain-like protease (*60*) (Fig. 3).

p53: "Guardian" of the Genome

One of the most important functions of p53 in cells is maintenance of genomic stability. This term encompasses all the mechanisms that ensure transmission of an intact genome from parental to descendent cells during mitosis. DNA replication, repair, and chromosome segregation should occur in an orderly fashion, and biochemical signal transduction pathways must ensure completion of each step before entering subsequent phases. Some of these pathways, known as cell cycle checkpoints, involve p53, either acting as a transcription factor or by its interaction with other proteins. p53 can thus be a direct participant in maintaining DNA integrity by acting in the mechanisms of homologous and illegitimate recombination (*61–63*), DNA repair (*32*), DNA replication (*64–66*), gene amplification (*67*), and chromosome segregation (*68–70*). p53 can also indirectly maintain DNA integrity by sensing abnormal cell cycle progression and maintaining cell populations with intact genomes through cell cycle arrest (allowing for DNA repair) or by eliminating damaged cells (inducing senescence or by stimulating apoptosis) (Fig. 4).

Loss of p53 Function in Cell Growth Arrest, Differentiation, or Apoptosis: Abnormal CNS Development and Neoplastic Transformation

p53 plays a central role in determining whether a cell must undergo differentiation, senescence, or apoptosis.

p53-dependent cell cycle arrest and apoptosis can be seen as indirect mechanisms by

which p53 accomplishes maintenance of genomic stability. Both pathways are induced by DNA damage, the ultimate result of which is the repair or elimination of DNA damaged cells. Therefore, they are two important mechanisms avoiding tumor initiation or progression, or both. p53-dependent apoptosis and cell differentiation are two crucial pathways of CNS development. Lack of p53 can sometimes result in severe developmental abnormalities leading to exencephaly.

p53 and Cell Cycle Arrest

p53 is able to block the cell cycle both at the G1 checkpoint and at the G2/M transition (*71–73*). The loss of cell cycle control functions normally assumed by p53 is believed to contribute to tumor development in the CNS. Upon p53 restoration in glioma cells cell cycle arrest is observed, which can be either a reversible arrest or an irreversible senescent-like event (*74,75*). At the molecular level, p53-dependent growth arrest is induced by p53 transactivating different cell cycle regulators, such as p21 and TGF-β (*76–79*). p21 arrests the cell cycle by inhibiting the activity of cyclin-dependent kinase complexes (*78*) and is the most important p53-induced cell cycle regulator. Indeed, human glioblastoma cells lacking p53 genes (LN-Z308) have low levels of p21, and transfection of wt p53 in such cells activates p21 expression and inhibits cell growth (*80,81*). Direct transfer of *CDKN1*, the gene encoding p21 in different glioma cell lines (U373MG, U87MG, GB-1), also induces growth arrest (*82*). Moreover, p21 overexpression is accompanied by a diminished malignant phenotype, as demonstrated in vivo using peripheral and intracerebral xenograft models (*82*). Accordingly, the introduction of the *CDKN1* gene in a rat glioma cell line was shown to induce growth arrest, cell susceptibility to radiation, and tumor necrosis (*83*). Nevertheless, the absence of *CDKN1* gene mutations in human gliomas suggests that it cannot be considered a tumor suppressor gene (*84*).

In other tumor models, it was shown that overexpression of one of the growth arrest specific genes (gas1) blocks cell proliferation in a p53-dependent manner, although p53 transactivating function was dispensable in this case (*85*). This may be related to the fact that p53 is also responsible for the transcriptional repression of different cell cycle inducer genes through its interaction with the TATA box binding protein (*23*), but these factors have not yet been studied in brain tumors.

p53 and Apoptosis

It is now common knowledge that p53 is able to trigger apoptosis in different human cells including undifferentiated neurons, oligodendrocytes and glioma cell lines (*86–89*). This mechanism is essential for the development of the central nervous system as well as in tumor prevention and treatment. Different stimuli like DNA damage, myc and adenovirus E1A expression and withdrawal of growth factors can trigger p53-dependent apoptosis (*1*).

Studies made on the molecular mechanisms of p53-dependent apoptosis result in unclear and contradictory data. Both the transactivating function of p53 and its capacity to repress gene transcription seem to be important to accomplish apoptosis (*90,91*). Indeed, p53 induces the expression of Bax and represses Bcl-2 (*92,93*) and, in a human glioblastoma, it was shown that p21 is a downstream mediator in p53-dependent apoptosis (*94*). Recently, it was proposed that p53 transactivating function can trigger apoptosis through induction of redox-controlling genes, which in turn increases reactive oxygen species (ROS), causing oxidative damage, which produces apoptosis (*95*).

Other data indicate that p53 transactivation function is dispensable for induction of apoptosis (*96*). Deletion of the N-terminal proline-rich domain of p53 abolishes p53-induced apoptosis, although the protein retains its transactivation capacity. This p53 domain could probably be determinant in inducing apoptosis by interacting with other proteins through its Pro-X-X-Pro motifs (*97,98*).

p53-dependent apoptosis plays an important role in the development of the CNS, when mat-

uration of the CNS involves massive scale death of neurons.

In vitro experiments show that apoptotic death of undifferentiated neurons and of oligodendrocytes is p53-dependent (*86–88,99,100*). High levels of Bax and reduced levels of Bcl-2 are found in some neurons before ischemic death; therefore, it is likely that a change in balance between these two molecules is a key event in p53-mediated neuronal death (*87*).

In vivo, a significant fraction of p53 knockout mice were found to die before birth. Analysis of these embryos showed that about 20% present a failure in closure of the neuronal tube, which results in exencephaly followed by anencephaly (*101,102*). The normal development of surviving p53 knockout mice shows that, in brain development, the missing p53 function is probably substituted by other proteins, perhaps one of the recently cloned p53 family members (*103,104*).

Because p53 is associated with neuronal damage and is involved in apoptotic death of oligodendrocytes (*86*), clarifying the role of p53 in the processes underlying neuronal and oligodendrocytic death should provide novel information in the understanding of CNS development, but also of certain CNS pathologies/injuries. Degenerative disorders, including Alzheimer's disease and brain trauma, involve neuronal cell death (*87*, and references therein), and multiple sclerosis is characterized by oligodendrocytic death (*105*). Accordingly, p53-dependent apoptosis seems to be the major cause of adrenalectomy-induced degeneration of hippocampal granule cells (*106*).

p53 in Differentiation

Clues as to the involvement of p53 in the differentiation processes are given by the observation of induction of several differentiation markers after p53 overexpression. For example, immunoglobulin chains μ and κ are induced in pre-B cells after p53 induction (*107*).

Within the context of the CNS p53 acts as a regulatory protein for the differentiation of neurons and oligodendrocytes in vitro. Subcellular localization of p53 from cytoplasm to nucleus occurs in oligodendrocyte progenitors at 24 h after the addition of differentiating medium. Subsequently, p53 nuclear staining decreases to basal levels in fully differentiated cells (*87*). These results were confirmed by observation of a block in neurite extension (marker of oligodendrocyte differentiation) after adding a dominant negative p53 protein to the cells (*87*). The physiological mechanism(s) by which differentiation signals may mediate nuclear translocation are unknown. Once in the nucleus, p53 may control differentiation by transcriptionally activating a specific subset of differentiation-related genes.

To examine when and where p53 might be important in development, p53 expression and transcriptional activity was followed during mice embryonic development using transgenic mice harboring a lacZ gene under the control of a p53-regulated promoter. The resulting data indicate that p53 is highly expressed in the early developing CNS, in undifferentiated cells, in neuroblasts, and in neurons (*99,100,108*). These results support a role for p53 in certain stages of CNS development, although the precise topography and dynamics of p53 expression in different brain areas have not yet been defined.

p53 Mutations in Tumors of the CNS

Analysis of *TP53* gene status and overexpression of its protein product have been well documented in primary CNS tumors (Fig. 2). Although the entire *TP53* gene is a good target for all different types of mutations, such as deletions, insertions, transitions, and transversions, a differential distribution of these classes of mutations can be observed along the gene. Although alterations truncating the protein, such as insertions and deletions, were found along the whole gene, point mutations that alter p53 function seem to be situated only in the hydrophobic core of the protein (87% in exons 5–8), where single base substitutions can compromise the protein conformation or function,

or both. The lack of point mutations outside the core of the protein is probably also the result of the fact that most investigators have focused their analyses on exons 5–8 (*109*). Additionally, of 250 potential sites for mutations present in the *TP53* gene, 25% of all mutations found in human tumors cluster at codons 175, 245, 248, 249, and 273. The preferential alteration of particular sites of a gene can have different reasons: (1) they may occur for structural and chemical reasons (repetitive sequences or CpG dinucleotides and susceptibility to carcinogenic agents); (2) they may be due to biochemical problems related to the transcription and repair machinery; (3) they may be biologically motivated; for example, some mutants may give a growth advantage to the cells.

Crystallographic studies distinguished two types of mutation sites. Some are directly involved in DNA binding and include the hot spot codons 248 and 273, whereas others are required for the stable folding of the protein such as codon 175. Moreover, this analysis evidenced that the frequency of TP53 point mutations decreases at increased distances from the biologically important structures of the gene product (*16*).

Statistical analysis of *TP53* gene mutations found in tumors of the CNS has shown that *TP53* mutations are mostly restricted to tumors of astrocytic origin (33%) (*110*). Recent data obtained with a more sensitive protocol to detect p53 mutations show even higher frequencies: 67% in anaplastic astrocytoma and 41% in glioblastoma multiforme (*111*). Lower mutation frequencies are found in glioblastoma, because p53 mutation appears to occur preferentially only in some subtypes (*112,113*). *TP53* gene mutations also occur frequently in primary CNS lymphomas (30%) (*114*) but are quite rare in oligodendroglioma (13%) and in medulloblastoma (11%) and are apparently absent in other tumors of the CNS.

Most *TP53* gene alterations are spontaneous GC-AT transversions arising by deamination of 5′ methylcytosine at CpG sites. There are no brain tumor-specific mutations; the three most frequent alterations are at codons 175, 248, and 273. The frequency of mutations differs somewhat since mutation at codon 273 is predominant, whereas in other human tumors the most frequently mutated codons are 248, 249, and 175 (*115*). Nevertheless, there are still no data indicating a specific role of these mutants in the genesis of astrocytic tumors.

More contradictory data were obtained in an effort to understand whether p53 mutation is an initial, early or late event in glioma tumorigenesis. Evidence for p53 mutation as an initiation event in glioblastoma derives from the finding of brain tumors in patients with germline p53 mutations, such as occurs in patients with multifocal glioma (*116*) and in families with Li-Fraumeni syndrome. These groups present a high incidence of tumors of the CNS (13%), most of which are astrocytomas (73%) (*117*). Additionally, the pattern of mutations in sporadic and inherited brain tumors is similar. The in vitro transformation of spontaneously immortalized cortical astrocytes of p53 knockout mice (*118,119*) gives additional strength to the theory that p53 mutation is an early initiation event in the formation and progression of astrocytomas. As a result of the early death of p53 knockout mice attributable to lymphomas and sarcomas, the causality of loss of p53 wt function in CNS tumors could not be demonstrated.

Genetic analysis of cell lines derived from gliomas induced in rats by *N*-ethyl-*N*-nitrosureas (ENU) showed high frequency of p53 mutations (*120,121*) in domains II-V (*120,121*). Immortalization and transformation of astroglial cells can also occur independent of p53 mutation (*120,121*). Either cell immortalization is induced by genes other than *TP53*, or p53 mutation is associated with later stages of tumorigenesis, or both.

Conclusions

During the past 10 years, the importance of p53 in tumor research has increased dramatically and p53 has become involved in a wide range of functions: safeguard of genome stabil-

ity, cell cycle arrest, differentiation, apoptosis, angiogenesis, and tumor cell invasion. Additionally, both biological and clinical analysis of p53 in tumors has demonstrated its particular importance in the most malignant type of primary brain tumor: astrocytoma. By contrast, for example, to carcinomas in which p53 mutation is a late event in the formation of the tumor, in astrocytoma there is considerable evidence that p53 alteration occurs early in the progression of the disease. Moreover, although the primary characterized function of p53 is as an oncosuppressor, in the brain p53 may also function as a regulator of CNS development. Lack of p53 may cause exencephaly, although in this disease, p53 absence can, in some cases, be compensated by other proteins. In both brain tumors and exencephaly, the capacity of p53 to induce apoptosis may be determinant in causing the disease. In the first case, as a way to eliminate genetically damaged cells; while in the second case, as a normal physiological process essential to the orderly development of the CNS. Therefore, the comprehension of p53 structure and regulation, as well as the molecular pathways of p53-dependent apoptosis, cell cycle arrest, and differentiation should bring us closer to gaining molecular insights into these severe diseases of the CNS.

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